REMARKS

Applicants request reconsideration of the present application in view of the foregoing amendments and the following remarks.

I. Status of the Claims

Claims 15 and 24-28 are presently pending in the application. Claim 15 has been amended to more particularly point out and distinctly claim the invention as a method of treating a patient suffering from an elevated blood level of ionized calcium accompanied with cachexia caused by interleukin-6 (IL-6) production. Support of the amendment of claim 15 is found in examples 2 and 3 of the specification, in particular, the paragraphs bridging pages 25 and 26 with reference to figure 15 and bridging pages 26 and 27 with reference to figure 18.

II. Rejection based on 35 USC §112, first paragraph

The Examiner has rejected claims 15, 24, 26 and 27 under 35 USC §112, first paragraph, for failing to meet the written description requirement. The Examiner asserts that disclosure limited to the use of PM-1 in a claimed method is not commensurate in scope with the claims drawn to generic antibodies that bind to the IL-6 receptor and interfere with IL-6 binding and signal transduction. Applicants respectfully traverse this rejection.

At the outset, Applicants would direct to the examiner's attention to the fact that claims presented here are directed to a method of treating a patient suffering from an elevated blood level of ionized calcium accompanied by cachexia caused by IL-6 production by using antibodies to IL-6 receptor, not to IL-6 receptor antibodies themselves. In fact, inventive features of the present invention lies in finding use of

antibodies to IL-6 receptors that are already known and recognized in the art. Thus, Applicants respectfully submit that identifying functional characteristics of antibodies to IL-6 receptors, as recited in claim 15, is enough for showing Applicants' possession of claimed invention at the time of filing.

Nonetheless, keeping the Written Description Guidelines in minds, Applicants explain below why one of ordinary skill in the art would have readily apprehend that a method using antibodies to IL-6 receptors having recited functional characteristics were in possession of Applicants as of filing date of the instant application.

According to the final guidelines of written description published January 5, 2001, in determining whether applicant was in possession of the claimed invention, a number of factors should be considered in addition to an actual reduction to practice of the claimed invention. Such factors include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Further, the guidelines state that, in contrast to the inventions in emerging and unpredictable technologies, in most technologies which are mature, and wherein the knowledge and level of skill in the art is high, a written description question should not be raised for original claims even if the specification discloses only a method of making the invention and the function of the invention.

According to the specification, gene sequences of human IL-6R and mouse IL-6R for producing antibodies are disclosed in European Patent Application, EP 325474 and in Japanese Unexamined Patent Publication 3 (1991), respectfully. Thus, an antigen, IL-6 receptor, has been isolated and characteristics or features of IL-6 receptor have been well known in the art.

Furthermore, the specification states that antibodies recited in the claimed invention are produced by the method known in the art, *e.g.*, conventional

immunization method, conventional cell fusion method and conventional screening method. Moreover, the specification illustrates MR16-1 and PM-1 antibodies that are already known in the art, as an example of such antibodies. See the specification at page 4, lines 12-16.

Thus, the totality of description of the specification clearly evidences that the level of skill and knowledge in the art of antibodies to IL-6 receptor at the time of filing was such that production of antibodies against a well-characterized antigen was conventional. That is, this is a mature technology where the level of skill is high and advanced.

In addition, the specification also clearly defines functional features of antibodies of the claimed invention as blocking signal transduction by IL-6 and to inhibit the biological activity of IL-6 by inhibiting the binding of IL-6-to-IL-6 receptor.

The article of Liautard *et al.*, is cited by the examiner to support the written description rejection. However, Liautard *et al.*, rather reflects high level of skill in the relevant art because it evidences that epitopes of IL-6 receptor have been recognized in the art before filing date of the application. Thus, Applicant respectfully submit that Liautard *et al.* should be considered as a reference showing that functional characteristics of antibody of IL-6 are well known in the art at the time of filing, rather than discounting Applicant's possession of claimed invention.

Considering the routine art-recognized method of making antibodies to fully characterized antigens, the well defined, the functional characteristics of antibody binding, and the fact that antibody technology is well developed and mature, one of ordinary skill in the art would have recognized that the spectrum of antibodies which bind to IL-6 receptor as well as a treatment method using such antibodies were in possession of Applicants at the time of filing of the instant application.

Therefore, the requirement that Applicants amend the claims to recite a method using a single IL-antibody, PM-1, would allow those of skill in the art to profit unfairly based on Applicants' contribution to the art. Accordingly, Applicants respectfully request withdrawal of the rejection.

III. Rejection based on 35 USC §103

The Examiner has rejected claims 15 and 24-28 as obvious over Emilie *et al.* ("Emilie") in view of Sato *et al.*("Sato"). More specifically, the Examiner asserts that it would have been *prima facie* obvious one of ordinary skill in the art to substitute the humanized PM-1 antibody for the antagonist of the IL-6 receptor used by Emilie in the treatment of cachexia, with a reasonable expectation of success from the teaching of Sato. Applicants respectfully traverse this rejection.

As an initial matter, all of the pending claims are now directed to the treatment of a patient suffering from an elevated blood level of ionized calcium accompanied by cachexia. Thus, the arguments will be limited to the applicability of the cited prior art against the amended claims.

Neither Emilie nor Sato teaches or suggests use of antibodies to IL-6 receptor to suppress elevation of blood level of ionized calcium, which is accompanied by cachexia. By contrast, the present inventors came to focus on the use of antibodies to IL-6 receptor based on findings that antibodies to IL-6 receptor contributes to not only treating cachexia but also suppressing an elevated blood level of ionized calcium accompanied thereby. See the specification at pages 25-27, figures 15 and 18.

The cited prior art provides no hint that antibodies to IL-6 receptor can affect a blood level of ionized calcium accompanied cachexia. Although both hypercalcemia showing increased blood levels of ionized calcium and cachexia are disorders commonly found in a late stage of cancer patients, these disorders are completely distinct in terms of their causes and symptoms. Although their causes are not

completely recognized, cancer cachexia is believed to be associated with a generalized increase in metabolism together with central effects on the hypothalamus while hypercalcemia may result from production of parathyroid hormone-like substance or local bone destruction depending on the type of cancer.

As a result, it is well understood that suppressing the blood level of ionized calcium does not necessarily result from treating cachexia. Thus, the prospect of suppressing an elevated level of ionized calcium accompanied by cachexia with antibodies to IL-6 receptor would not have been apparent to one of ordinary skill in the art, in view of the prior art of record that is silent in this aspect. Furthermore, Emilie and Sato evidence no motivation in the prior art for using antibodies to IL-6 receptor to suppress an elevated blood level of ionized calcium accompanied by cachexia. Accordingly, there is no *prima facie* case of obviousness.

Furthermore, suppressing an elevated blood level of ionized calcium accompanied by cachexia is itself an unexpected result which could not have been predicted from disclosure of the prior art, alone or in combination. The attainment of unexpected results or properties is a powerful demonstration of patentability. *See U.S. v Adams*, 383 U.S. 39, 51-52 (1966); *Lindemann Maschinenfabrik v. American Hoist and Derrick Co.*, 730 F.2d 1452, 1461 (Fed. Cir 1984). Applicant's demonstration of unexpected results further establishes patentability of the claimed invention.

Accordingly, Applicants respectfully request withdrawal of the obviousness rejection.

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In view of the foregoing amendments and remarks, Applicants respectfully request favorable reconsideration and allowance of the pending claims. If there are any issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner hereby is respectfully invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

Date August 28, 2001

By [signature] Reg. No. 34485

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Marked up rewritten claims:

15. (Twice Amended) A method of treating a patient [having] suffering from an elevated blood level of ionized calcium accompanied by cachexia caused by interleukin-6 (IL-6) production comprising administering to said patient a therapeutically effective amount of an antibody to an IL-6 receptor in a pharmaceutically acceptable carrier [to treat said cachexia] to suppress elevation of blood level of ionized calcium and wherein the therapeutically effective amount blocks signal transduction by IL-6 and inhibits the binding of IL-6 to the IL-6 receptor.